

Appln. No. 10/759,519

Final Office Action Office Action dated December 22, 2006

Amendment under 37 C.F.R. 1.116 dated June 22, 2007

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Listing of the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Currently amended) A method for determining a haplotype of a subject comprising the steps of:
 - (a) diluting a nucleic acid sample from the subject into a single molecule dilution;
 - (b) amplifying the diluted single molecule dilution ~~[[and]]~~ in a multiplex amplification reaction with at least ~~[[two]]~~ four different primer pairs designed to amplify at least ~~[[two]]~~ four nucleic acid regions each comprising at least ~~[[two]]~~ one polymorphic site~~[[s]] in the nucleic acid template;~~
 - (c) genotyping the at least ~~[[two]]~~ four nucleic acid regions ~~that wherein each region contains at least one polymorphic site in the single nucleic acid molecule wherein the genotyping is performed using primer extension and mass spectrometric detection;~~ ~~[[and]]~~
 - ~~[[d]]~~ (d) repeating steps a-c from the same nucleic acid sample to obtain 12-18 genotype replicas from the same subject and thereafter comparing the at least 12-18 genotype replicas to determine the haplotype; and
 - ~~[[d]]~~ (e) determining the haplotype from the genotypes of the at least ~~[[the]]~~ four polymorphic sites to obtain a haplotype for the subject.
2. (Cancelled)
3. (Currently amended) The method of claim ~~[[2]]~~ 1, further comprising comparing the haplotype with a haplotype from a control or a database of haplotypes from controls to determine association of the haplotype with a biological trait.
4. (Currently amended) The method of claim 1, wherein the at least ~~[[two]]~~ four polymorphic sites contain a polymorphism that is a single nucleotide polymorphism.

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5. (Currently amended) The method of claim 1, wherein the polymorphism is at least four polymorphic sites contain a polymorphism selected from a deletion, an insertion, a substitution or an inversion.
6. (Currently amended) The method of claim 1, wherein the at least ~~[[two]]~~ four polymorphic sites contain a polymorphism ~~that is a combination~~ wherein each of the polymorphisms is of one or more markers selected from the group consisting of a single nucleotide polymorphism, deletion, an insertion, a substitution or an inversion.
7. (Cancelled)
8. (Cancelled)
9. (Currently amended) A method of diagnosing a disease condition or disease susceptibility by determining a disease related haplotype in a subject comprising the steps of:
 - (a) diluting a nucleic acid sample from the subject into a single molecule dilution;
 - (b) amplifying the diluted single molecule dilution ~~[[and]]~~ in a multiplex amplification reaction with at least two primer pairs designed to amplify a region comprising at least two polymorphic sites in the nucleic acid template;
 - (c) genotyping the polymorphic sites in the single nucleic acid molecule wherein the genotyping is performed using primer extension and mass spectrometric detection;
 - ~~[[d]]~~ (d) repeating steps a-c from the same nucleic acid sample to obtain 12-18 genotype replicas from the same subject and thereafter comparing the at least 12-18 genotype replicas to determine the haplotype;
 - ~~[[d]]~~ (e) determining the haplotype from the genotype of at least two polymorphic sites to obtain a haplotype for the subject; and
 - ~~[[e]]~~ (f) comparing the haplotype of the subject to known disease-associated haplotypes, wherein a match in the sample haplotype with a

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disease-associated haplotype indicates that the subject has the disease or that the subject is susceptible for the disease.

10. (Cancelled)

11. (Cancelled)

12. (Currently amended) A method of determining a haplotype of a subject comprising the steps of:

- (a) treating a nucleic acid sample from the subject with a composition that differentially affects an epigenetically modified nucleotide in the nucleic acid sample to effectively create polymorphisms based on the epigenetic modification;
- (b) diluting the treated nucleic acid sample into a single copy dilution;
- (c) amplifying the diluted nucleic acid sample using at least ~~[[two]]~~ four different primer pairs in a multiplex amplification reaction;
- (d) genotyping the amplified sample, wherein genotyping is performed using primer extension and mass spectrometric detection; [[and]]
- ~~(e) repeating steps b-c from the same treated nucleic acid sample to obtain 12-18 genotype replicas from the same subject and thereafter comparing the at least 12-18 genotype replicas; and~~
- ~~[[e)] (f) determining the haplotype of the subject from the genotyped sample.~~

13. (Cancelled)

14. (Cancelled)

15. (Original) The method of claim 12, wherein the epigenetically modified nucleotide is a methylated nucleotide.

16. (Original) The method of claim 15, wherein the nucleic acid sample is treated with bisulfite.

17. (Currently amended) A method of determining a haplotype in a subject comprising the steps of:

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- (a) digesting a nucleic acid sample from the subject with a methylation-sensitive restriction enzyme so that either unmethylated DNA or methylated DNA is left intact, depending on which enzyme is used;
- (b) diluting the digested nucleic acid sample to a single molecule concentration;
- (c) amplifying the diluted and undiluted nucleic acid sample with at least two different primer pairs in a multiplex amplification reaction;
- (d) genotyping the amplified samples, wherein genotyping is performed using primer extension and mass spectrometric detection; ~~[[and]]~~
- ~~(e) repeating steps b-c from the same treated nucleic acid sample to obtain 12-18 genotype replicas from the same subject and thereafter comparing the at least 12-18 genotype replicas; and~~
- ~~[[e]]~~ (f) determining a haplotype of a methylated nucleic acid wherein at least one polymorphic marker next to the methylation site, together with the methylation site, constitutes a haplotype.

18. (Cancelled)

19. (Cancelled)